

FORM PTO-1390 (Modified)
(REV 11-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES

145865.00013

DESIGNATED/ELECTED OFFICE (DO/EO/US)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

CONCERNING A FILING UNDER 35 U.S.C. 371

New U.S. National Stage Application
10/031854INTERNATIONAL APPLICATION NO.
PCT/IN99/00055INTERNATIONAL FILING DATE
October 14, 1999PRIORITY DATE CLAIMED
July 26, 1999

TITLE OF INVENTION

A SYNERGISTIC COMPOSITION FOR THE TREATMENT OF LIVER AND LIVER ASSOCIATED AILMENTS
AND A PROCESS FOR PREPARING THE SAME

APPLICANT(S) FOR DO/EO/US

Ashok RAJGARHIA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☒ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Application Data Sheet; Verified Statement Claiming Small Entity Status; Response to Written Opinion
dated June 26, 2001; PCT/RO/101, PCT/ISA/220, PCT/IPEA/401, PCT/IPEA/408, and PCT/IPEA/416

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.101) New U.S. National Stage Application	INTERNATIONAL APPLICATION NO. PCT/IN99/00055	ATTORNEY'S DOCKET NUMBER 145865.00013
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24. The following fees are submitted:				CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :					
<input checked="" type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO				\$1040.00	
<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO				\$890.00	
<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO				\$740.00	
<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)				\$710.00	
<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)				\$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$1,040.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				\$0.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	4 - 20 =	0	x \$18.00	\$0.00	
Independent claims	1 - 3 =	0	x \$84.00	\$0.00	
Multiple Dependent Claims (check if applicable). <input type="checkbox"/>				\$0.00	
TOTAL OF ABOVE CALCULATIONS =				\$1,040.00	
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				\$520.00	
SUBTOTAL =				\$520.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).				\$0.00	
TOTAL NATIONAL FEE =				\$520.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). <input type="checkbox"/>				\$0.00	
TOTAL FEES ENCLOSED =				\$520.00	
				Amount to be refunded	\$
				charged	\$

- a. ☒ A check in the amount of \$520.00 to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-1682. A duplicate copy of this sheet is enclosed.
- d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Powell, Goldstein, Frazer & Murphy LLP
P.O. Box 97223
Washington, D.C. 20090-7223
202-624-3974


SIGNATURE

Mr. Richard Wilder
NAME

31,202
REGISTRATION NUMBER

January 24, 2002
DATE

Applicants or Patentee: **Mr. Ashok Rajgarhia**

For: ***A synergistic composition for the treatment of Liver and Liver associated ailments and process of preparing the same***

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL
ENTITY STATUS (37 CFR 1.9(f) and 1.27(b) – INDEPENDENT
INVENTOR**

As below named invention, I/We hereby declare that I/We qualify as an independent Inventor(s) as defined in 37 CFR 1.9 (c) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office with regard to the invention entitled "***A synergistic composition for the treatment of Liver and Liver associated ailments and process of preparing the same***" as described in the specification filled herewith.

I/We have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who could not be classified as an independent inventor under 37CFR 1.9 (c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37CFR 1.9 (d) or a non-profit organization under 37CFR 1.9 (e).

Each person, concern or organization to which I/We have assigned, granted, conveyed, or licensed or am/are under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

☐ no such person, concern or organization

☐ persons, concerns or organizations listed below*

- NOTE: Separate verified statements are required for each named person, concern or organization having rights to the invention averring to their status a small entities (37 CFR 1.27)

Full Name **Mr. Ashok Rajgarhia**

Address C/o Rajgarhia Paper Mills Pvt. Ltd., 15, Exchange Place, Calcutta-700 001, India.

☒ Individual ☐ Small Business Concern ☐ Nonprofit organization

I/~~We~~ acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying the earliest of the issue fee or any maintenance fee due after the date on which status as small entity is no longer appropriate (37 CFR 1.28(b))

I/~~We~~ hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.



Mr. Ashok Rajgarhia

Date: 18/01/02

**" A SYNERGISTIC COMPOSITION FOR THE TREATMENT OF
LIVER AND LIVER ASSOCIATED AILMENTS AND A PROCESS
FOR PREPARING THE SAME"**

The present invention relates to a synergistic composition for the treatment of liver and liver associated ailments and a process for preparing the same.

Background

Liver is an important organ in the human body and is responsible for its well being. It helps in detoxifying many exogenous toxic substances present within the human body, which are consumed as drugs or with food. These toxic wastes reduce the efficiency of the liver as a blood purifier. Liver also undergoes frequent attacks by viral infections such as hepatitis.

India has the second largest pool of HBV carriers in the world. It has a population of over 45 million HBV carriers and 15 million HCV carriers. One fourth of these are at risk to suffer from chronic liver diseases and its lethal complications, such as cirrhosis or even liver carcinoma. Coupled with the burden of HBV related liver diseases, there is an ever increasing patient load due to Hepatitis C. Screening of all the blood before use for HIV, is still a distant reality and this contributes to a significant increase in chronic liver diseases in India.

Therefore it has become absolutely essential to develop an effective therapeutic strategy to tackle this problem.

In allopathy, at present no specific drug is available for providing adequate cover for protection of or preventing liver from various infections and diseases. In Ayurveda, many plant extracts are known, which have a hepatoprotective effect. However, the effect of such crude plant extracts as used in Ayurveda is slow by virtue of presence of

other components which may prevent full action of the active ingredient/component.

One of the plant extracts used as medicine for treatment of liver diseases is the root extract of plant *Glycyrrhiza glabra* (liquorice).

Said extract contains flavonoids, saponins, oligo-glycosides, phenolic compounds and glycyrrhizic acid. *Glycyrrhiza glabra* is known to have four actions which help in treatment and prevention of liver diseases (Sub acute liver failure, cirrhosis liver with activity)

Cyto-protective action - This helps in fortifying the cell, which enables the cell to protect itself from virus / infection.

Anti-inflammatory and Immunomodulatory action - This helps in reducing the inflammation of the organ and help modulate the organ to function normally. It also has cholerectic action.

Anti-oxidant action - Helps in preventing replication of virus.

Anti-viral action - The combined effect of the above helps in preventing replication of virus, thus there is reduction of viral load over a period of continued administration of the drug.

The activity of the extract of *Glycyrrhiza glabra* is also due to the action of beta glycyrrhizinic acid at the level of complement component C2.

However, liquorice extract when taken in large quantities for prolonged periods, causes high blood pressure (hypertension), water retention, weight gain due to pseudoaldosteronism and possibly heart complications.

Extract of roots of *Picrorrhiza Kurroa* have also been recommended as a hepatoprotective agent for protection of liver toxicity caused by hepatotoxic agents such as alcohol, carbon tetra chloride, viruses and parasites. Roots of *Picrorrhiza kurroa* contain glycosides, kutkin

(kulkosides and picosides) and other organic acids such as vallanic and cinnamic acids.

The extract of Picrorrhiza roots is bitter and it increases gastric secretion, diminishes the force of heartbeat and reduces the blood pressure.

Therefore there was a need to develop a synergistic composition having a pleasant flavour which would have hepatoprotective action, against the virus and at the same time enhance the protective action against hepatotoxic agents such as those in food, drug and alcohol.

The object of the present invention was therefore to provide for a synergistic composition having enhanced hepatoprotective action with reduced side effects.

Yet another object of the present invention is to provide for a composition having hepatoprotective effect against both viruses and hepatotoxic agents.

The aforesaid object is achieved by the present invention, which relates to a synergistic composition for the treatment of liver and liver associated ailments comprising:

extract of Glycyrrhiza glabra and Picrorrhiza kurroa in ratio 2-1:1-3 by weight.

The said composition may be mixed with excipients for tableting.

The present invention also provides a process for preparing a synergistic composition for the treatment of liver and liver associated ailments comprising:

- preparation of extract from the roots of Glycyrrhizia Glabra and Picrorrhiza kurroa,

- optimization of the extract of *Glycyrrhiza glabra* to ensure the maximum content of glycyrrhizin.
- optimization of the extract of *Picrorhiza kurroa* to ensure maximum content of Kutkin.
- mixing the two extracts obtained in ratio 2-1:1-3 at ambient temperature and pressure to obtain the composition.

The extract of *Glycyrrhiza glabra* is mixed with extract of *Picrorhiza kurroa* preferably in the ratio 1.25 : 2.

The extracts of *Glycyrrhiza glabra* and *Picrorhiza kurroa* may be prepared in any known manner.

The extract of *Glycyrrhiza Glabra* may also be prepared after treating the powdered roots with a non polar solvent in the proportion of 1:5 by volume for removing unwanted components such as saponins, pigments and lipids in the supernatant. The residue obtained is mixed in 3-5 times volume of hot water at 60-90° C and constantly stirred for 3-5 hours. This water mixture is acidified and the residue extracted and dried in such a way that optimum concentration of Glycyrrhizin is obtained. The extract is standardized on TLC plates to obtain a definite number of components in each batch of the extract.

The extract of *Picrorhiza kurroa* may also be obtained after treatment of the dried powdered roots of the plants with petroleum ether in the proportion 1:3 by volume. The residue extracted with alcohol (60%) and left in cold water to remove / reduce the content of undesired components and concentrated to dryness to get optimized extract of *Picrorhiza kurroa*. The extract can be standardized by TLC to get same constituents in each batch of extract.

The composition of the herbal extracts in the present drug will enhance the hepatoprotective activity and at the same time reduce harmful side effects.

Method of Optimization

Optimization of Liquorice extract:

Glycyrrhizin content in liquorice root ranges from 3-6%. A standard curve is plotted of different UV readings taken from the after carrying out TLC test on of different conc. of pure Glycyrrhizin. The extract obtained from liquorice are put on TLC and the concentration of Glycyrrhizin in the extract is measured on UV and quantified with the help of the standard curve plotted above.

Optimization of Picrorhiza kurroa extract:

Similar procedure is carried out for optimizing the extract of Picrorhiza kurroa extract. Optimization is done to a stage of 40-70% content of Glycyrrhizin / Kutkin in the extracts.

The present invention will now be described with reference to foregoing examples:

Example 1:

The extract of Glycyrrhiza glabra is optimized at 50% Glycyrrhizin content. The extract of Picrorhiza kurroa is optimized at 40% kutkin content. 100mg of Glycyrrhiza glabra extract is mixed with 20mg of Picrorhiza Kurroa extract to prepare the composition. Excipients are added to make a tablet form.

Example 2:

The extract of Glycyrrhiza glabra is optimized at 60% Glycyrrhizin content. The extract of Picrorhiza kurroa is optimized at 40% kutkin content. 84mg of Glycyrrhiza glabra extract is mixed with 31.5 of Picrorhiza Kurroa extract to prepare the composition. Excipients are added to make a tablet form.

DOSAGE:

Adult	- -	2 Tablets Three times / day
Child	-	1 Tablet three times / day

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Claims:

1. A synergistic composition for the treatment of liver and liver associated ailments characterized by:
extract of Glycyrrhiza glabra and Picrorhiza kurroa in ratio 2-1:1-3 by weight.
2. A composition as claimed in claim 1 characterized in that the extract of Glycyrrhiza glabra is mixed with extract of Picrorhiza kurroa in the ratio of 1.25 : 2.
3. A process for preparing a synergistic composition as claimed in claim 1 characterized by :
 - preparation of extract from the roots of Glycyrrhizia Glabra and Picrorhiza kurroa.
 - optimization of the extract of Glycyrrhiza glabra to ensure the maximum content of glycyrrhizin.
 - optimization of the extract of Picrorhiza kurroa to ensure maximum content of Kutkin.
 - mixing the two extracts obtained in ratio 2-1:1-3 at ambient temperature and pressure to obtain the composition.
4. A process as claimed in claim 3 wherein characterized in that the extract of Glycyrrhiza glabra is mixed with extract of Picrorhiza kurroa in the ration 1.25 : 2.

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

A Synergistic composition for the treatment of liver and liver associated ailments and process of preparing the same.

The specification of which (check one)

- ☒ is attached hereto.
☐ was filed on _____ as Application
 Serial No. _____ and was amended on
 _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, section 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATION(S)

			<u>Priority Claim</u>	
<u>660/Cal/99</u>	<u>India</u>	<u>26th July, 1999</u>	<u>X</u>	
(Number)	(Country)	(Day/Month/Year filed)	Yes	No
<u>661/Cal/99</u>	<u>India</u>	<u>26th July, 1999</u>	<u>X</u>	
(Number)	(Country)	(Day/Month/Year filed)	Yes	No

DECLARATION AND POWER OF ATTORNEY

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States Provisional application(s) listed below:

PRIOR PROVISIONAL APPLICATIONS

(application serial number)

(Month / Day / Year filed)

(application serial number)

(Month / Day / Year filed)

I hereby claim the benefit under Title 35, United States Code, section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, section 112. I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status – patented, pending, abandoned
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint Richard C. Wilder, Reg. No. 31,202, and each principal, attorney of counsel, associate and employee of Powell, Goldstein, Frazer & Murphy, LLP, who is a registered Patent Attorney, my attorney with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. I request the Patent and Trademark Office to direct all correspondence and telephone calls relative to this application to Powell, Goldstein, Frazer & Murphy, LLP, P.O. Box 97233, Washington, D.C. 20090-7223, (202) 547-0066.

Full name of sole or first inventor: Mr. Ashok Rajgarhia

Inventor's signature: Ashok Rajgarhia

Date: 18/01/02

Residence: Rajgarhia Paper Mills Pvt. Ltd., 15, Exchange Place, Calcutta-700 001, India

Citizenship: Indian

Post Office Address: Same as residence